Treatment of Thrombophlebitis

HOWARD B. KIRTLAND JR., *M.D.*, ROLAND G. BROWN, *M.D.*, and RICHARD T. McDONALD, *M.D.*, San Diego

• **Venous stasis, injury or alteration of the intima and alterations in the coagulability of the blood are the three most common etiologic factors in thrombophlebitis. Usually at least two of these factors must be present before the clinical manifestations of the disease develop.**

A plan of treatment based on correcting these three factors has been used in over 250 cases of thrombophlebitis, and it is believed that a significant decrease was brought about in the acute and long term disability and in the occurrence of complications.

The program consists of absolute bed rest in a hospital for about a week, elevation of the foot of the bed, administration of anticoagulants and adenosine-5-monophosphate for at least six weeks, progressive ambulation after the fourth day of treatment, with avoidance of prolonged standing and sitting, and adequate elastic support. Treatment must be continued until the patient has returned to full, normal activity and all signs of phlebitis have disappeared.

THROMBOPHLEBITIS, especially of the veins deep in the legs, is a relatively common, acutely disabling disease. Complications and sequelae can cause death or long and severe disability. Because it has a decided tendency toward progression and recurrence, an understanding of etiologic delineations is necessary for successful treatment.

Attempts to treat thrombophlebitis as a disease with a single cause have brought about very little benefit. In observing a series of cases of thrombophlebitis, it soon becomes apparent that there are multiple etiologic factors and that in most instances at least two or three of them are present before the disease develops to a clinical stage. It is obvious that not all the etiologic factors are known, but the three major and most common factors are those pointed out by Virchow[13] in 1860 and recently emphasized by Keefer.[7] These are venous stasis, injury or alteration of the intima, and alterations in the coagulability of the blood. A plan of treatment based on correcting these three factors has been used in over 250 cases of thrombophlebitis dealt with by the authors in the last five years. We believe that this plan of treatment has resulted in a significant decrease in the acute and long term disability and complications of thrombophlebitis. In addition, observation of the patients and their response to treatment has suggested some additional etiologic factors and forms of treatment. Many failures of treatment in the past have been due to discontinuance of it when the patient left the hospital. Certainly, if treatment is worthwhile, it should be continued until there has been completion of the process of organization, recanalization and endothelialization of the occluded veins and compensation of the collateral venous and lymphatic channels.

STASIS AND EDEMA

Elevation of the foot of the bed on shock blocks 6 to 8 inches high, as advocated by deTakats and Jesser,[4] is one of the most effective methods of improving venous return from the pelvis and lower extremities. Wright and Osborne[16] showed that this about doubles the venous flow rate. It also promotes lymphatic drainage. Pillows are not good for the purpose because they become dislodged and obstruct venous return. Elevation of the lower half of the bed while the upper part remains flat does not aid drainage in the pelvic area. Cranking the feet up and the head down causes painful hyperextension of the lumbosacral region. While frequent deep breathing and coughing, early ambulation and vigorous exercise of the legs prevent stasis and are excellent prophylactic measures, they have no place in the initial treatment of acute thrombophlebitis because of the danger of causing an embolus.

On the diagnosis of acute thrombophlebitis of the deep veins of the legs, we prescribe absolute bed rest with the foot of the bed elevated on 6-inch shock blocks. The head is kept dependent most of the time, but is elevated for meals and during use of the bedpan. After adequate prothrombin levels have been obtained and all of the edema and most of the pain and tenderness have cleared, gradually increasing ambulation is started. This is usually about the third or fourth hospital day. Walking is for five minutes four times the first day, ten minutes four times the second day, and then more and more. When patients return home they may walk as much as they wish, but for at least three weeks they should avoid prolonged sitting or standing in one position. At home,

Presented before the Section on General Surgery at the 89th Annual Session of the California Medical Association, Los Angeles, February 21 to 24, 1960.

elevation of the foot of the bed is continued for two to six weeks or as long as there is any remaining edema in the leg or foot on awakening in the morning. The patients are encouraged to obtain work that combines walking and sitting and are instructed to walk a few minutes of every hour while on automobile, plane or train trips.[3]

In addition to elevation, edema is controlled by rubberized elastic support, which has been shown by Wilkins and associates[14] to increase the venous linear flow rate five-fold. This support is usually in the form of a 4-inch bandage from the toes to below the knee, and a 6-inch bandage from below the knee to mid-thigh. The bandages are rewrapped at least every eight hours. If after two to three weeks there is no significant edema of the thigh, the upper bandage is discontinued. Elastic support to the level of the knee is worn during the day for at least six weeks and as long as there is any edema in the lower legs or ankle at the end of the day or if there is discomfort on dependency.

If the swelling or discomfort is mild, tailor-made elastic stockings are substituted for the bandages at the end of six weeks. Patients are encouraged to lie down and elevate their legs at 45 degrees for 15 to 30 minutes several times a day. Also, swimming and wading are very effective in reducing edema. In patients who have recurrent thrombophlebitis, after a previously inadequately treated episode, heavier support such as gum rubber Rochester bandages or Aero-pulse® boots are sometimes necessary.

Another factor in the production of edema and venous stasis is the reflex vasospasm that often accompanies thrombophlebitis. In cases in which this is severe enough to cause the low temperature and pulselessness of the leg which raises the question of arterial insufficiency, a liter of 5 per cent alcohol with 50 to 75 mg. of Priscoline®[8] given intravenously over a two to three-hour period will usually bring about warming of the leg and foot with bounding pulses and considerable relief of pain. If spasm is a problem, after the adequacy of the arterial blood supply has been ascertained in this way, a heat cradle is kept over the legs. If rest pain or cellulitis or lymphangitis is a problem, the elastic bandages are omitted and the leg is encased in bulky hot compresses applied from toes to groin and kept warm by a heat cradle at 100° to 105° F. Usually after two to three days the hot compresses can be discontinued and elastic bandages applied. Winsor's[15] demonstration of the ability of the phenothiazine derivatives to block conditioned vasomotor reflexes may be of help to us here as well as in the treatment of certain sequelae.

Adenylic acid or My-B-Den® therapy in the form of an adenosine-5-monophosphate sustained action gel intramuscularly, as originally advocated by Boller[1] and Rottino,[11] was given to about 75 per cent of the patients in the present series. This is a muscle enzyme substance which, among its actions, is a mild vasodilator. We feel that it has produced considerable objective and subjective benefit and we plan to test this impression with a double blind study. This substance does not appear to have any effect on the intravascular clot, but seems to decrease and keep at a minimum the perivascular inflammation and the associated induration and neuritis. This effect is most apparent in superficial thrombophlebitis in which induration of the perivascular fat is readily palpable. There also appears to be a more rapid clearing of edema. Forty milligrams of the sustained action gel is given intramuscularly daily for three days, then 20 mg. daily until the patient is discharged from hospital, and then 20 mg. three times a week for six weeks. Sublingual tablets were tried but seemed to be ineffective. Rectal suppositories seemed to us to be as effective as intramuscular injections, but apparently they will not be made commercially available due to excessive cost of production.

Of course other factors which cause stasis, such as heart failure and hypotension, are vigorously treated.

INTIMAL INJURY

While it is generally recognized that stasis and altered coagulability of the blood often persist after the onset of thrombophlebitis and unless treated will result in extension of the process, the possibility of further intimal injury is often overlooked. Unevenly wound tight elastic bandages, prolonged flexion of the edematous leg, resting the involved leg on a small ridge, even on a firm pillow, all can cause further intimal injury. Injury of a different type is that produced by reaction to the clot lying in the lumen of the blood vessel both distal and proximal to the area of actual thrombophlebitis or by infection in the intravascular clot. Recognition and avoidance of the first group of these possibilities plus the measures undertaken for the control of stasis, edema and altered coagulability are adequate to control further injury except in the case of infection. The great majority of cases of deep thrombophlebitis and many cases of superficial thrombophlebitis are not associated with infection. However, perivascular infection can result in all three of the factors of intimal injury, stasis, and altered blood coagulability and thus can be the cause of thrombophlebitis and of its persistence or extension.[9] The superficial veins lie in tissues more liable to infection secondary to injury, folliculitis or lymphatic transmission, and thus are more frequently the site of thrombophlebitis due to infection. The edema secondary to thrombophlebitis of course predisposes to infection which in turn can cause further phlebitis.

After the onset of deep phlebitis the soft intravascular clot is an excellent culture medium and can result in the conversion of a transient bacteremia by a virulent organism (from a superficial infection or introduced by intramuscular injection) into serious septicemia. We have seen such a course of events result in serious septicemia which kept a young woman near death for over two months before recovery without residual or recurrence during subsequent pregnancy and surgical operation.

In all cases of thrombophlebitis in which the patient continues to run a high or spiking fever or has evidence of concomitant lymphangitis and regional lymphadenitis on an infectious basis, a blood culture is obtained and antibiotic sensitivity tests are carried out. After the blood for culture is obtained, the patient is started on antibiotic therapy, usually with one of the drugs that are effective against most strains of staphylococcus and streptococcus. It should be emphasized that our use of antibiotics in thrombophlebitis has been the exception and not the rule.

During the first half of this series of cases, we determined the erythrocyte sedimentation rate before the start of treatment. There was no significant correlation between the result of this test and the severity of the disease and it was not of any aid in arriving at a diagnosis in questionable cases.

ALTERNATION IN COAGULABILITY

The clotting of blood and the prevention of clotting in the living state involve complex processes and factors which even today are not completely understood. However, it is known that an increase in any one of a number of coagulant factors can result in a greater clotting tendency. Conversely, an increase in any of a number of anticoagulant factors not only can negate this increased clotting tendency but also can cause a considerable decrease in the ability of the blood to clot. Knowledge of these various factors is important in prophylaxis of thrombophlebitis, but, from the standpoint of treatment, exact knowledge of the clotting mechanism is not necessary. Small but significant alterations in the coagulability of blood have been difficult to measure with the usual tests. However, silicone coagulation times, prothrombin consumption and heparin retarded clotting times seem to reflect these changes more readily. We have not yet used these tests extensively but have hopes that they will be of aid to us in determining when treatment should be instituted to prevent or abort an early attack of thrombophlebitis, particularly in patients with a history of recurrent attacks. Observation of patients with recurrent attacks has borne out the observations by others that corticosteroids[5] and stress[6,12] can produce rapid changes (within minutes or hours) in the coagulability of blood. Thus, in one patient recurrent, full blown episodes have accompanied the forced marriage of her wayward son, stressful family reunions, and the like. Likewise alteration of the constituents of the blood have also resulted in increased clotting tendencies. Polycythemia with its accompanying increase in thrombocytes can result in rapid and extensive propagation of the thrombus. Conversely, as was pointed out by Quick[10] once a clot has been formed, anemia with its increased clot retraction and consequent increased local concentration of thromboplastin also can cause the thrombus to enlarge. Except for the obvious necessity for correction of such factors as anemia, the only really practical method available for altering the coagulability of blood is the use of anticoagulants such as heparin and the coumarin drugs. While they do not necessarily result in correction of the specific factor which has caused increased coagulability of the blood, in most (but not all) cases they bring about a favorable reversal of the ratio of coagulation factors to anticoagulation factors in the blood. They do not dissolve the clot. However, Burt[2] showed they do usually effectively prevent further propagation of the clot and speed its resolution. Heparin is probably the superior anticoagulant, but it is expensive and administration of it is difficult and time consuming. We have used it only in cases in which an embolus has already occurred or there are other factors making it advisable. Even then we shift to the coumarin drugs after a few days. While there are many excellent drugs, we prefer Coumadin sodium® because of the relatively short lag period and the predictability of dosage. Before it is given, a prothrombin concentration base line is obtained. Then an initial dose of 30 to 60 mg. (usually 40 mg.) is given. Twelve to 18 hours later an additional 10 mg. is given. Thirty-six hours after the initial dose a second determination of prothrombin concentration is carried out and almost invariably it is in the therapeutic range (15 to 25 per cent). Daily dosage is then based on the result of the prothrombin concentration while the patient is in the hospital. This is usually 10 mg. a day, but has varied from 2.5 to 25 mg. After discharge of the patient from the hospital, anticoagulant therapy is continued for at least six weeks (prothrombin concentrations being determined weekly) and until all signs of active phlebitis have disappeared and the patient has returned to full, normal activity. We believe it is important to continue coumarin therapy during the period of organization, recanalization and endothelialization of the clot. With increasing activity the requirements of anticoagulant drug are usually increased. When the base line prothrombin concentration is depressed significantly or a subsequent level is greatly

depressed due to overdosage or hypersensitivity, the concomitant administration of vitamin K_1 oxide (5 mg. orally), with one or two doses of Coumadin® has resulted in stabilization of response and greatly increased ease of management.

That anticoagulant therapy does not solve all problems was well illustrated by the case of one of the patients in the present series who had a second pulmonary embolus after six months of continuous anticoagulant therapy. The prothrombin concentration value at the time of embolization was 15 per cent.

While the foregoing program of initial hospitalization, elevation, progressive ambulation, elastic support, adenylic acid and anticoagulant therapy is somewhat more vigorous and prolonged than that usually advocated, we believe it has produced better results, both in our hands and those of others reporting series.

The usual period of stay in hospital has been seven days. The period of disability has been three to five weeks, and the incidence of recurrence and sequelae such as chronic edema, varicose veins, ulcers and stasis dermatitis has been low. We have frequently seen femoral neuritis at about three to six weeks from the onset of the phlebitis and late reflex vasospasm, both of which have responded well to treatment in most cases. Our experience with fibrinolysin has been limited but we have been impressed with its possibilities, especially in cases of early small clot or pulmonary embolus. We have used two types of intramuscular trypsin but have noted no benefit from either of them.

The regimen herein described modified but did not control, the course of the disease in a few cases (less than 5 per cent of the series). In two of these the addition of inferior vena cava ligation solved the problem, but we hope that a careful analysis of the others with recurrent symptoms and recurrent acute attacks may give us a better understanding of the entire disease process.

We strongly believe that the appearance of incompetent perforating veins, varicosities and recurrent stasis ulcers in the late phlebitic state are indications for surgical treatment.

3505 Fourth Avenue, San Diego 3 (Kirtland).

REFERENCES

1. Boller, R., Rottino, A., and Pratt, G. H.: Therapeutic action of muscle adenylic acid on ulcers and dermatitis associated with varicose or phlebitic veins; follow up report, Angiology, 3:260-266, June 1952.

2. Burt, C. C., Wright, H. P., and Kubik, M.: Clinical tests of a new coumarin substance; a report to the Medical Research Council, Brit. M. J., 2:1250-1254, Dec. 3, 1949.

3. Dale, W. A.: Ligation of inferior vena cava for thrombophlebitis, Surgery, 43:24-44, Jan. 1958.

4. deTakats, G., and Jesser, J. M.: Pulmonary embolism: suggestions for its diagnosis, prevention and management, J.A.M.A., 114:1415-1421, April 13, 1940.

5. Foley, W. T., and Wright, I. S.: Color atlas and management of vascular disease, Appleton-Century-Croft, Inc., New York, 1959, p. 36.

6. Friedman, M., Rosenman, R. H., and Carrol, V.: Changes in the serum cholesterol and blood clotting time in men subjected to cyclic variation of occupational stress, Circulation, 17:852-861, May 1958.

7. Keefer, C. S.: Thrombosis and thrombophlebitis, J. Med. Assn. of Georgia, 47:55-64, Feb. 1958.

8. Kirtland, H. B., Jr., Brown, R. G., and McDonald, R. T.: Intravenous alcohol and tolazoline HCl in the evaluation of the ischemic limb. To be published.

9. Lutz, B. R., Lutton, G. P., and Alsers, R. P.: White thromboembolism in the hamster cheek pouch after trauma, infection and neoplasia, Circulation, 3:339-351, March 1951.

10. Quick, A. J.: A new concept of venous thrombosis, Surg. Gynec. & Obst., 91:296-300, Sept. 1950.

11. Rottino, A., Boller, R., and Pratt, G. H.: Therapeutic action of muscle adenylic acid on ulcers and dermatitis associated with varicose or phlebitic veins; preliminary report, Angiology, 1:194-200, April 1950.

12. Schneider, R. A.: Recurrent thrombophlebitis: An experimental study of life situations and emotions and the clotting time and relative viscosity of the blood, Am. J. Med. Sc. 222:562-578, Nov. 1951.

13. Virchow, R.: Cellular pathology as based on physiological and pathological histology, Robert M. DeWitt, New York, 1860.

14. Wilkins, R., Mixter, G., Stanton, J. R., and Litter, J.: Elastic stockings in prevention of pulmonary embolism, N.E.J.M., 246:360-364, March 1952.

15. Winsor, T.: Conditioned vasoconstrictive responses of digital vessels, A.M.A. Arch. Surg., 76:193-199, Feb. 1958.

16. Wright, H. P., and Osborne, S. B.: Effect of posture on venous velocity measured with 24 NaCl, Brit. Heart J., 14:325-330, July 1952.